Sustained clinical responses to tyrosine kinase inhibitor sunitinib in thyroid carcinoma

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The limited therapeutic options available for patients with metastatic papillary thyroid carcinomas (PTC) and follicular thyroid carcinomas (FTC) necessitates the development of novel therapies. Identification of somatic rearrangements of the tyrosine kinase domain of the *RET* gene in PTC have improved our understanding of thyroid tumorigenesis. Sunitinib is active against the *RET* kinase and has both antineoplastic and antiangiogenic properties. Its role in the treatment of patients with thyroid carcinoma has yet to be evaluated in clinical trials. Two patients with progressive metastatic thyroid carcinoma (case 1: PTC, and case 2: FTC) were enroled in a phase I clinical trial to evaluate positron emission tomography (PET) in the monitoring of response to sunitinib. Tumour biopsies and PET were performed at baseline and 4 weeks after the commencement of sunitinib. Activation of the *RET* kinase pathway was evaluated using immunohistochemistry (IHC) and western blot analysis of total phosphorylated tyrosine and downstream signalling targets of the *RET* pathway. Both patients demonstrated sustained clinical responses to sunitinib over a duration of 4 years. In case 1, (PTC) PET confirmed evidence of a partial metabolic response, and IHC and western blot analysis demonstrated inhibition of the *RET* kinase pathway posttreatment. In case 2, (FTC) PET confirmed stable disease after sunitinib. IHC staining of the tumour showed low total phosphorylated tyrosine staining at baseline which did not change after treatment. These case studies highlight potential activity of sunitinib in patients with metastatic thyroid carcinoma. Sunitinib seems to be a promising agent in the treatment of thyroid cancers and this requires validation in future clinical trials. *Anti-Cancer Drugs* 19:547–552 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2008, **19**:547–552

Keywords: *RET*, sunitinib, thyroid cancer

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Received 17 December 2007 **Revised form accepted** 11 February 2008

Introduction

Thyroid malignancies arising from the follicular epithelium are classified into two distinct morphological categories, papillary and follicular carcinomas. Papillary carcinomas are the most common, accounting for 80% of all thyroid malignancies, whereas follicular carcinomas constitute only 5–10%. Recent advances in molecular biology have improved our understanding of the pathogenesis of these malignancies. Somatic rearrangements of the tyrosine kinase domain of the *RET* gene with the 5′-end of heterologous genes are found in some papillary thyroid carcinomas (PTCs) with the resulting chimeric sequence (RET/PTC) exerting oncogenic activity [1]. RET/PTC is capable of ligand-independent activation by constitutive dimerization, leading to autophosphorylation of intracellular tyrosine residues and subsequent activation of downstream signal transduction pathways that regulate growth and cell survival [1]. RET/PTC rearrangements are found in up to 33% of sporadic papillary carcinomas and in 60–80% of those occurring after irradiation [2,3]. In contrast, RET/PTC rearrangements have not been identified in patients with follicular thyroid carcinomas (FTC) [3].

Sunitinib (SU011248) is an oral, multitargeted, tyrosine kinase inhibitor with antiangiogenic and antineoplastic activity owing to inhibition of vascular endothelial growth factor receptor (VEGFR), platelet derived growth factor receptor (PDGFR), foetal liver tyrosine kinase receptor 3 (FLT3) and the stem cell factor receptor (KIT) [4]. In addition, a recent preclinical study has confirmed that sunitinib is a highly effective inhibitor of the RET/PTC oncogenic kinase suggesting a role for this agent in the treatment of RET/PTC-positive papillary thyroid cancers [5]. Interestingly, sunitinib also demonstrates toxicity to the normal thyroid, with over 80% of patients developing hypothyroidism [6]. It is not clear if this toxicity is related to inhibition of RET kinase. In phase I clinical trials, sunitinib demonstrated activity in patients with a variety of solid malignancies; however, currently there is no clinical data reporting activity in thyroid carcinoma [7]. We describe two case studies of patients with

metastatic thyroid carcinoma who have demonstrated sustained clinical responses to sunitinib.

Methods

Two patients with metastatic thyroid carcinoma (case 1: PTC, and case 2: FTC) were enroled in a phase I clinical trial designed to evaluate positron emission tomography (PET) in the monitoring of response to sunitinib [8]. Tumour biopsies and imaging with [^{18}F]fluorodeoxyglucose (FDG) PET were performed at baseline and 4 weeks after the commencement of sunitinib therapy. Activation of the *RET* kinase pathway was evaluated using immunohistochemistry and western blot analysis.

Positron emission tomography imaging

In this prospective trial, standardized acquisition of PET studies was stipulated. All patients were prepared for the FDG-PET scan by fasting for at least 6 h. Blood glucose levels were measured to ensure levels below 10 mmol/l. Patients were then injected with between 320 and 400 MBq of FDG and rested lying on a bed for at least 1 h before scanning. Using a hybrid PET-computerized tomography (CT) scanner (Discovery LS, GE Medical Systems, Millwaukee, Wisconsin, USA), a 4-slice helical mode CT scan was acquired during quiet respiration with parameters as required for routine PET attenuation correction and coregistration. These were 140 kV_p and 80 mA, 5.0 mm slices with an interval of 4.25 mm. This was followed by PET scanning encompassing the neck thorax, abdomen, pelvis and proximal thighs. PET scanning was performed in two-dimensional mode with five or six bed positions at 5 min per step. The transaxial field of view was the same for both CT and PET. PET emission data were reconstructed using an ordered subset expectation maximization algorithm and attenuation correction derived from CT data. The PET, CT and coregistered PET/CT images were then reviewed on a dedicated review workstation (GE Entegra, GE Medical Systems).

Immunohistochemistry

Formalin-fixed tissue was imbedded, cut into 3-μm sections, de-waxed and probed with antibodies using standard procedures. Antigens were retrieved in Tris-EDTA buffer (pH 9.0) for 2 min in a pressure cooker and slides were loaded onto a DAKO Autostainer (Dako North America, Inc., Carpinteria, California, USA) with all subsequent procedures carried out on the machine at room temperature. Endogenous peroxidase activity was quenched in 3% H_2O_2 (10 min) before incubation for 30 min with antiphosphorylated tyrosine antibody (Cell Signaling Technology antibody 9411, Mouse monoclonal antibody P-Tyr-100) at 1 : 1200 dilution. Bound antibody was detected using the polymer linked detection system (EnVision + Mouse, DAKO) with DAB + (DAKO) visualization. Sections were counterstained with haematoxylin.

Western blotting

Quantitative western blotting was performed as previously described using the Li-Cor Odyssey Infrared Imaging System (Li-Cor Biosciences, San Jose, California, USA) [9]. Primary antibodies used at 1 : 1000 dilution were antiphosphorylated tyrosine (Cell Signaling Technology antibody 9411), antiphosphorylated S6 (Cell Signaling Technology antibody 2211), antiphosphorylated p44/42 mitogen-activated protein kinase (Thr202/Tyr204, Cell Signaling Technology antibody #9101), antiphosphorylated SHP2 (Tyr580, Cell Signaling Technology antibody #3754) and antiactin (Clone C4 at 1 : 20 000 dilution; MP Biomedicals, Livermore, California, USA). Secondary antibodies used at a 1 : 5000 dilution were Alexa Fluor 680 goat anti-rabbit IgG (Molecular probes, Grand Island, New York, USA) and IRDye 800 anti-mouse IgG (Rockland Immunochemicals, Inc., Gilbertsville, Pennsylvania, USA).

Case 1

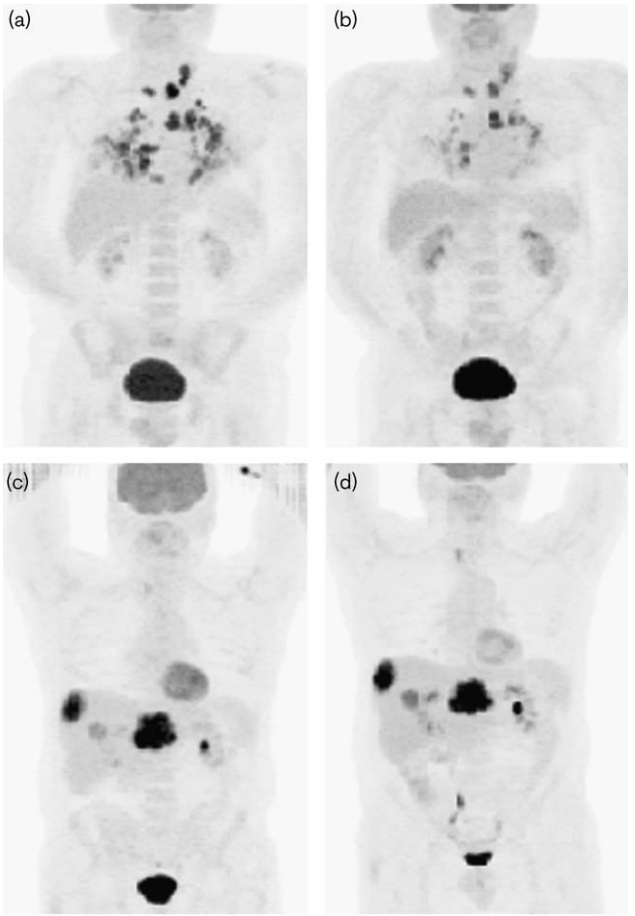
A 51-year-old man presented with a solitary thyroid nodule and underwent a partial thyroidectomy. Histopathology confirmed a PTC. After surgery, a routine ^{131}I scan revealed residual thyroid activity in the neck and he subsequently underwent treatment with ^{131}I ablation. One year later, asymptomatic pulmonary metastases were detected on routine imaging. Further ^{131}I imaging was performed; however, the pulmonary metastases were not iodine-avid. Continued observation with regular imaging documented slow progression of the pulmonary lesions on CT scans.

Six years after his original diagnosis, he developed symptoms of a hoarse voice, dry cough and shortness of breath on exertion. At this stage he was referred to a specialized cancer centre for management. Imaging with FDG-PET showed extensive PET-avid thyroid carcinoma metastases in the mediastinum and lungs bilaterally, residual tumour in the thyroid bed, left cervical lymphadenopathy and a new sacral bony metastasis (Fig. 1a). The left cervical lymphadenopathy was biopsied confirming metastatic PTC.

Treatment with sunitinib was commenced at a dose of 50 mg daily for 4 weeks every 6 weeks in the setting of the phase I clinical trial [8]. One month after the commencement of treatment, a repeat FDG-PET scan was performed confirming a partial metabolic response with a qualitative decrease in both the extent and intensity of the abnormalities noted in the mediastinum, lungs, thyroid bed and left lateral neck (Fig. 1b). In addition, a repeat biopsy of the left cervical lymph node demonstrated tumour fibrosis with a small focus of residual metastatic carcinoma.

Immunohistochemical staining showed a reduction in total phosphorylated tyrosine after treatment (Fig. 2a and b).

Fig. 1



[^{18}F]Fluorodeoxyglucose-positron emission tomography (FDG-PET) imaging at baseline and after treatment with SU11248. Patients were treated with sunitinib for 4 weeks and FDG-PET scans were performed at baseline and in the fourth week of sunitinib therapy. FDG-PET of case 1 papillary thyroid carcinoma (PTC) at baseline (a) and after sunitinib therapy (b). FDG-PET of case 2 follicular thyroid carcinoma (FTC) at baseline (c) and after sunitinib therapy (d). Note an FDG response was obtained for case 1 (PTC) but not case 2 (FTC).

Cellular protein was then analysed by western blot analysis. Total tyrosine phosphorylation (Fig. 2e) and phosphorylation of downstream signalling targets (ERK, S6 and SHP2) were all shown to be inhibited posttreatment, similarly to TT cells treated with sunitinib (Fig. 3). We were not able to detect RET protein in tumour samples with commercially available antibodies.

Twelve months after commencing sunitinib, he had a generalized seizure and was found to have small cerebral metastases. He was commenced on an anticonvulsant and subsequently has had very slow progression of his cerebral metastases, not requiring any intervention. The patient has now continued on sunitinib for a total of 4 years. No evidence of progression of his lung metastases over this time has been observed. Toxicities have included plantar erythema with associated hyperacanthosis, and hypertension. However, overall the treatment has been well tolerated.

Case 2

A 65-year-old man initially diagnosed with prostate cancer after the incidental detection of an elevated prostate-specific antigen (PSA) at 25 µg/l underwent a radical prostatectomy. Twelve months after surgery his PSA began to rise and he was referred to a specialized cancer centre for consideration of salvage radiotherapy. Before considering radiotherapy, staging investigations including a bone scan and CT scan were performed. These confirmed the presence of multiple liver metastases and a solitary skull metastasis. Unexpectedly, biopsies of the liver and skull metastases revealed metastatic FTC. The patient's history was significant for removal of a thyroid nodule 7 years before which had been reported as benign. He had not undergone regular follow-up since this time and the original histopathology could not be retrieved for comparison.

After the diagnosis of metastatic FTC, a complete thyroidectomy was performed. Postoperatively, ^{131}I scanning demonstrated that the metastatic disease was noniodine avid and ablative ^{131}I therapy was therefore not undertaken. Sunitinib was subsequently commenced at a dose of 50 mg for 4 weeks of every 6 weeks in the setting of the phase I clinical trial [8]. FDG-PET was performed before commencement of treatment and the metastatic disease was PET-avid. One month after the commencement of treatment, a repeat FDG-PET confirmed stable disease and no new sites of disease activity (Fig. 1c and d).

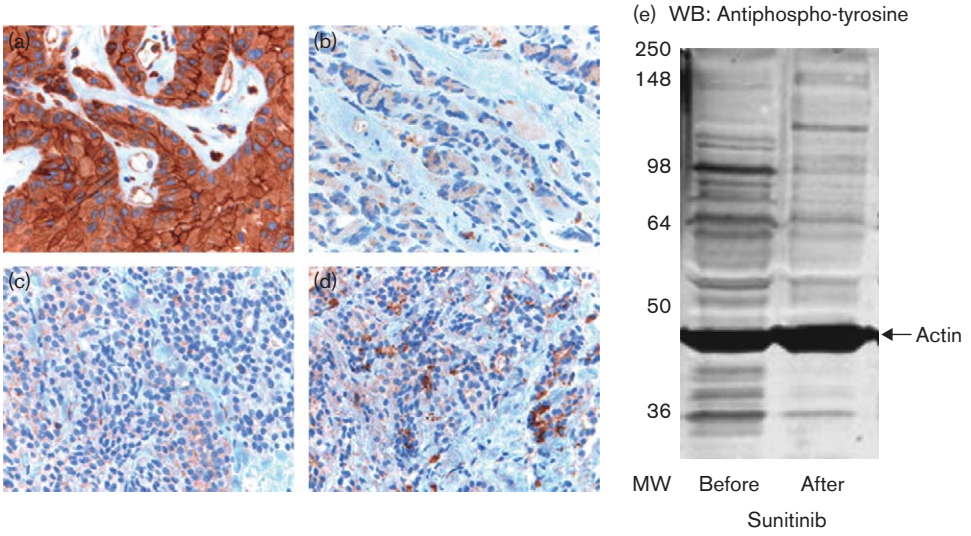
Immunohistochemical staining of the tumour showed low total phosphorylated tyrosine staining at baseline that did not change after treatment (Fig. 2c and d). Fresh frozen tumour samples for case 2 were not available, therefore, no western blot data were generated.

Treatment with sunitinib has now been continued for 4 years with no evidence of disease progression. Toxicities have included lethargy, stomatitis, hypertension and plantar erythema. The patient did not undergo salvage radiotherapy for his prostate cancer, but was commenced on goserelin injections. His PSA remains well controlled, and there has been no evidence of progressive metastatic prostate cancer since this time.

Discussion

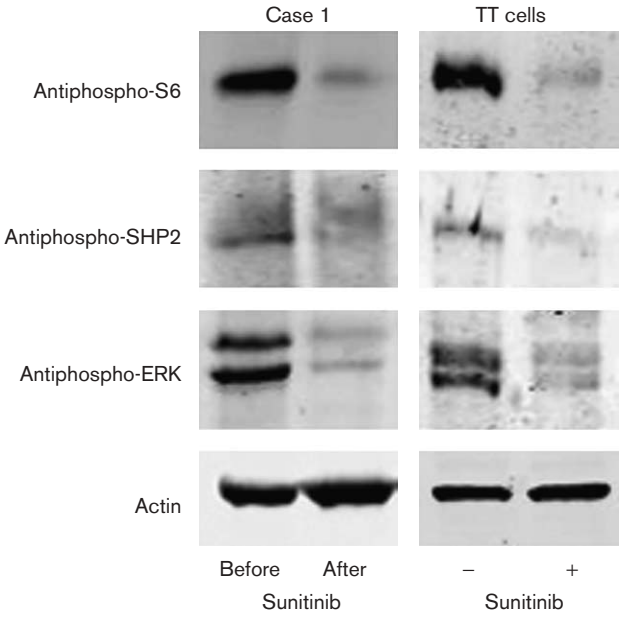
PTC and FTC are among the most curable malignancies, with the combination of aggressive surgery, radioactive iodine therapy and supraphysiologic thyroid hormone replacement. However, approximately 10–15% of patients will eventually develop metastatic disease [11]. The most

Fig. 2



Immunohistochemistry of the tumour sections. Patients were treated with sunitinib for 4 weeks and biopsies were performed at baseline and in the fourth week of sunitinib therapy. Immunohistochemical staining with an antibody to total phosphorylated tyrosine was performed at baseline on case 1 (a) and case 2 (c), and after sunitinib therapy on case 1 (b) and case 2 (d). Note marked inhibition of staining with antiphosphotyrosine in case 1 (papillary thyroid carcinoma) but not case 2 (follicular thyroid carcinoma). Data shown are from high-power ($\times$ 200) microscopic fields. Decreased total phosphotyrosine level in case 1 after sunitinib treatment [after; (e)] was also seen by western blot analysis as compared with baseline level [before; (e)]. MW, molecular weight; WB, western blotting.

Fig. 3



Western blot analysis of RET/papillary thyroid carcinoma (PTC) pathway. Western blot analysis of case 1 PTC at baseline (before) and after sunitinib therapy (after). Note the inhibition of downstream signalling targets (ERK, S6 and SHP2) posttreatment. TT, control (medullary thyroid cancer cell line containing activated RET [10]) cells not treated (–) or treated with 0.1 μm sunitinib (+) for 30 min. Antiphos, antiphosphorylated.

common sites of metastases include the regional lymph nodes, lungs and bone. Patients with metastases are most effectively treated with therapeutic doses of ^{131}I but this is not feasible if metastatic deposits are not iodine-avid. Chemotherapy has limited activity in differentiated thyroid cancer [12,13]. The 10-year overall survival rate after the discovery of metastatic disease is approximately 40% [11]. To improve treatment outcomes in this disease, there is a need for the development of targeted therapies focused on the molecular pathogenesis of these malignancies.

The identification of the RET/PTC oncogene in PTC has made a significant contribution to the understanding of thyroid tumorigenesis and represents an ideal target for the development of novel treatments. The RET/PTC rearrangement results in elevated kinase activity, which can be inhibited by small-molecule kinase inhibitors that compete with ATP thereby obstructing autophosphorylation and signal transduction downstream from the targeted kinase. Multitargeted tyrosine kinase inhibitors that have already shown activity against *RET* include the anilinoquinazoline ZD6474, the pyrazolopyrimidines PP1 and PP2, AMG-706 and the 2-indolinone derivative RPI-1 [14–19]. Recently, the indolinone kinase inhibitor sunitinib has also been shown to be active against the RET/PTC tyrosine kinase in preclinical studies [5]. In addition, sunitinib has been shown to selectively target

VEGFR, PDGFR, KIT and FLT3, resulting in both anti-angiogenic and antineoplastic properties [4].

The two current case studies highlight the potential activity of sunitinib in patients with metastatic thyroid carcinoma. The initial case of a patient with metastatic PTC demonstrated evidence of both clinical and biological antitumour activity after the commencement of sunitinib. In addition, this case highlights the role of FDG-PET imaging in monitoring disease activity. Imaging with PET is being increasingly explored to detect the full biological effects of new targeted agents as it allows assessment of the functional aspects of tumour status such as metabolic activity through quantification of glucose uptake. In this case study, the response seen on PET imaging was confirmed by biochemical evaluation of the tumour. These studies demonstrated inhibition of total phosphorylated tyrosine and the phosphorylated downstream signalling targets (ERK, S6 and SHP2). This is in keeping with the expected activity of sunitinib in preventing autophosphorylation of the RET/PTC kinase and subsequently inhibiting downstream signal transduction pathways. Importantly, this patient who had clear evidence of progressive pulmonary metastases at the time of study entry, has had no subsequent progression of his pulmonary metastases while on treatment for over 4 years. The slow progression of his cerebral metastases, without progression of his lung or nodal metastases, raises the possibility of lower concentrations of sunitinib in the central nervous system owing to the blood–brain barrier. Nevertheless, the long follow-up and the continued benefit are unique and provide an insight into the potential advantages of treatment with sunitinib over time.

The second case of a patient with metastatic FTC also demonstrated prolonged stable disease after treatment with sunitinib. Although this patient had evidence of a durable clinical response, there was no evidence of a biological response to treatment via the RET/PTC pathway. The pathogenesis of FTC is not mediated through the RET/PTC oncogene and the genetic rearrangement has not been identified in this histological subtype of thyroid cancer [3]. *RET* does not appear to be expressed in thyroid follicular cells lacking RET/PTC activation [1]. In contrast, the mechanism of disease stabilization in the case described may relate to the antiangiogenic properties of sunitinib, which targets VEGFR and PDGFR in the tumour vasculature. In support of a role for antiangiogenic agents in the treatment of thyroid cancer other novel small-molecule kinase inhibitors targeting VEGF, AMG-706, axitinib and sorafenib have recently shown activity in patients with PTC and FTC in phase I/II clinical trials [20–22].

The combined effect of targeting *RET* in thyroid cancer cells, and targeting VEGFR and PDGFR in the tumour vasculature may provide distinct advantages and offer a focussed route for translating the unique profile of sunitinib into a meaningful treatment for patients with metastatic thyroid cancer. To date, phase III clinical trials of sunitinib have been reported for the treatment of renal cell carcinoma and gastrointestinal stromal tumours [23,24]. The current evidence suggests a role for sunitinib as a promising agent in the treatment of thyroid cancers and this requires further validation in future clinical trials.

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